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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,767	05/27/1999	NICK GIANNOUKAKIS	A32362	5337

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/320,767	GIANNOUKAKIS ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This Action is in response to the communication filed on 7/22/05. The amendment filed 7/22/05 is acknowledged. The amendment has been entered. Claims 31, 35 and 39 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 31, 35 and 39 are examined herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Hunger et al. (European Journal of Immunology, 1997; Vol. 27, pages 255-261) for the reasons of record which are reiterated below for convenience.

Hunger teaches a transgenic mouse wherein all of the pancreatic β cells of the mouse comprise a nucleic acid that encodes and expresses a soluble type I tumor necrosis factor (TNF) alpha receptor that binds to TNF-alpha and inhibits TNF-alpha signaling in the cell (e.g., see abstract; p. 255; p. 257). Therefore, the soluble type I TNF-alpha receptor is a dominant negative TNF-alpha receptor. It is noted that the instant claims are not explicitly drawn to a

transgenic animal cell; however, given the broadest reasonable interpretation, the claim (i.e. a mammalian β cell comprising a recombinant nucleic acid molecule encoding and expressing a soluble type I TNF alpha receptor decoy protein) reads on a transgenic mouse pancreatic β cell that comprises a recombinant nucleic acid molecule that encodes and expresses the soluble TNF-alpha receptor.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muruve et al. (Transplantation, 1997; Vol. 64, pages 542-546) in view of Hunger et al. (European Journal of Immunology, 1997; Vol. 27, pages 255-261) for the reasons of record which are reiterated below for convenience.

The instant claims are drawn to methods comprising introducing into a β cell a nucleic acid molecule encoding a soluble type I TNF alpha receptor decoy protein and transplanting the β cell into an individual to reduce β cell dysfunction (claim 31), including β cell apoptosis (claim 35).

Muruve teaches that an adenoviral vector can be used to express a gene of interest in a pancreatic β cell for an extended period of time (e.g., see abstract, p. 542; p. 545, last two paragraphs). Furthermore Muruve teaches that the pancreatic β cell comprising the adenoviral vector can be transplanted into an individual such that the transplanted β cell expresses the gene of interest encoded by the adenoviral vector expresses said gene of interest for an extended period of time. As such, Muruve teaches an adenoviral vector that can be used for ex vivo gene therapy to express a therapeutic gene of interest in a pancreatic β cell.

Muruve does not teach that the adenoviral vector can be used to deliver and express a soluble TNF-alpha receptor dominant negative protein.

However, Hunger teaches that expressing a soluble TNF-alpha dominant negative receptor protein in mouse pancreatic β cells reduces β cell dysfunction that results in diabetes (including β cell apoptosis) compared to β cells that do not express the soluble TNF-alpha receptor protein.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Muruve such that the adenoviral vector expressed the a soluble TNF-alpha dominant negative receptor protein to make the claimed invention with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modification because (1) Muruve teaches, "using the replication deficient adenovirus, it is possible to express foreign proteins in pancreatic islets for extended periods of time without effecting their function in glucose homeostasis" (See p. 545, last paragraph), and (2) Hunger teaches that expressing soluble TNF-alpha receptor dominant negative protein in a β cell, "results in the complete protection... against a variety of in vivo pathological conditions mediated by TNF release... [β cells] bearing this transgene fail to develop diabetes..." (See p 255, last paragraph).

Response to Arguments

Applicant's arguments filed 7/22/2005 have been fully considered.

With respect to the rejection of claims under 35 USC 112, 2nd paragraph, the amendment is sufficient to overcome the rejection. As such, the rejection has been withdrawn.

With respect to the rejection of claims under 35 USC 102(b), Applicants arguments filed 7/22/2005 have been fully considered, but are not persuasive. Applicants submit that Hunger does not teach all of the limitations of the present invention. Applicants point out that anticipation requires that each and every element of the rejected claims be disclosed in a single prior art reference. Applicants note that Hunger discloses transgenic mice expressing a soluble TNF receptor which neutralizes bioactive TNF-α. Applicants contend that in contrast, claim 39 recites, "a soluble type I tumor necrosis factor alpha receptor decoy protein." Applicants assert that the specification defines decoy proteins "are capable of competing... for receptor binding but which fail to activate the signaling activity of the receptor" and point to the specification at page

15, lines 4-6. Thus, applicants contend, the soluble TNF receptor disclosed in Hunger binds to TNF-α, preventing it from binding to the membrane-bound TNF receptor, whereas the soluble type 1 tumor necrosis factor alpha receptor decoy proteins of claim 39 bind to the membrane bound TNF receptor, competing with TNF-α. Applicants assert that the soluble TNF receptor of Hunger is not the same as the soluble type I tumor necrosis factor alpha receptor decoy protein of claim 39.

In response, it is acknowledged that anticipation requires that each and every element of the rejected claims be disclosed in a single prior art reference. In the instant case, the Examiner disagrees with the Applicants that Hunger does not teach each and every element of the claims. Applicants assert that the specification defines decoy proteins as "capable of competing... for receptor binding but which fail to activate the signaling activity of the receptor" and point to the specification at page 15, lines 4-6. However, the specification page 15, lines 1-17 states:

> "In an embodiment of the invention, the activity of IL-1-beta can be regulated at the level of receptor binding using, for example, nucleic acid molecules encoding competitive antagonists of IL-1-beta. Such antagonists include but are not limited to the naturally occurring interleukin-1 receptor antagonist protein (IL-1Ra; also referred to as IRAP), soluble interleukin-1 receptor "decoys" that are capable of competing with wild type IL-1-beta for receptor binding but which fail to activate the signaling activity of the receptor **and soluble type I tumor necrosis factor alpha receptors** (Ghivizzani S C et al., 1998, Proc. Natl. Acad. Sci USA 95:4613-8)." (Emphasis added).

Therefore, the specification does not explicitly define decoy proteins such that the type 1 tumor necrosis factor alpha receptor decoy proteins of claim 39 are limited to soluble TNF proteins that bind to the membrane bound TNF receptor. Furthermore, the specification does explicitly indicate that the IL-1-beta antagonists include soluble type I tumor necrosis factor alpha receptors. Therefore, claim 39 is not limited to a type 1 tumor necrosis factor alpha receptor decoy protein that bind to the membrane bound TNF receptor as asserted by Applicants.

Given the broadest reasonable interpretation consistent with the specification, the claims encompass a soluble type I TNF-alpha receptor. Hunger teaches a soluble type I TNF-alpha receptor, thus Hunger does teach each and every element required by the claim.

Therefore, Applicants arguments are not persuasive and the rejection is maintained.

With respect to the rejection of claims under 35 USC 103(a) as being unpatentable over Muruve in view of Hunger, Applicant's arguments filed 7/22/2005 have been fully considered but they are not persuasive. Applicants submit that the Examiner has not set forth *prima facie* case of obviousness. Applicants assert that there is no suggestion or motivation to combine the references. Applicants argue that Hunger does not teach a type 1 tumor necrosis factor alpha decoy receptor. Applicants also assert that there would not have been a reasonable expectation of success because Hunger teaches a transgenic mouse that has consistently high expression of the soluble TNF-alpha receptor and a person of ordinary skill in the art would not be reasonably able to predict that the method of Hunger would work if expression was changed from a soluble TNF-alpha receptor to a receptor decoy protein and if expression was limited to beta cells. Applicants also contend that the references alone or in combination do not teach all of the limitations of the claims because neither teaches a TNF-alpha decoy receptor as required by the claim.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the combine the references because (1) Muruve teaches, "using the replication deficient adenovirus, it is possible to express foreign proteins in pancreatic islets for extended periods of time without effecting their function in glucose homeostasis" (See p. 545, last paragraph), and (2) Hunger teaches that expressing soluble TNF-alpha receptor protein in a β cell, "results in the complete protection... against a variety of in vivo pathological conditions mediated by TNF release... [β cells] bearing this transgene fail to develop diabetes..." (See p 255, last paragraph).

In response to Applicants argument that Hunger does not teach a TNF-alpha decoy receptor. As indicated above, the specification does not explicitly define decoy proteins such that the type 1 tumor necrosis factor alpha receptor decoy proteins of the claims are limited to soluble TNF proteins that bind to the membrane bound TNF receptor. Furthermore, the specification does explicitly indicate that the IL-1-beta antagonists include soluble type I tumor necrosis factor alpha receptors. Therefore, the claims are not limited to a type 1 tumor necrosis factor alpha receptor decoy protein that bind to the membrane bound TNF receptor as asserted by Applicants. Given the broadest reasonable interpretation consistent with the specification, the claims encompass a soluble type I TNF-alpha receptor. Hunger does teach a soluble type I TNF-alpha receptor, thus Hunger does teach a soluble decoy receptor encompassed by the claims. Furthermore, given the broadest reasonable interpretation consistent with the specification, the cited references do teach each and every limitation of the claims.

With respect to Applicants arguments that there would not have been a reasonable expectation of success because Hunger teaches a transgenic mouse that has consistently high expression of the soluble TNF-alpha receptor and a person of ordinary skill in the art would not be reasonably able to predict that the method of Hunger would work if expression was changed from a soluble TNF-alpha receptor to a receptor decoy protein and if expression was limited to beta cells, Applicants arguments have been fully considered but are not persuasive. First, since Hunger teaches a soluble TNF-alpha receptor that meets the limitations of the claims (as indicated above), there is no requirement that the expression be changed to a different soluble TNF-alpha receptor. Second, the teaching of Hunger are sufficient to indicate that expressing a soluble TNF-alpha receptor in pancreatic β cells would reduce β cell dysfunction that results in diabetes (including β cell apoptosis) compared to β cells that do not express the soluble TNF-alpha receptor protein, even if all of the pancreatic β cells of the subject did not express the soluble receptor protein. One would expect the vector taught by Muruve can be used to express the soluble TNF-alpha receptor gene of Hunger in pancreatic β cells for an extended period of time and that the extended expression of the soluble TNF-alpha receptor would reduce β cell dysfunction.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore Applicants arguments are not persuasive and the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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